



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/445, 47/14	A1	(11) International Publication Number: WO 97/49402 (43) International Publication Date: 31 December 1997 (31.12.97)
(21) International Application Number: PCT/EP97/03236 (22) International Filing Date: 19 June 1997 (19.06.97) (30) Priority Data: 96201782.8 27 June 1996 (27.06.96) EP <i>(34) Countries for which the regional or international application was filed:</i> DE et al. (71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors; and (75) Inventors/Applicants (for US only): VLAMINCK, Kathleen, Marie, Jeanne, Alice [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). FRANÇOIS, Marc, Karel, Jozef [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). HEYNS, Christiane, Gabriella, Gerarda, Maria [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).		(81) Designated States: AL, AM, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: SUSTAINED RELEASE SUFENTANIL COMPOSITIONS (57) Abstract <p>The present invention concerns sustained release sufentanil compositions for intramuscular administration, the preparation of said compositions and the use of said compositions for inhibiting pain, in particular post-operative pain, in animals, particularly in companion animals.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

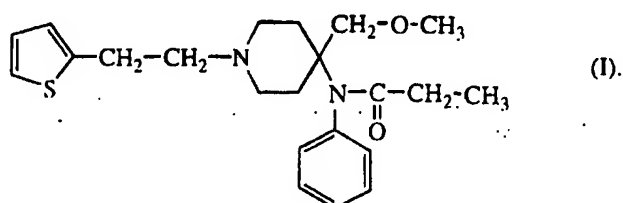
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

SUSTAINED RELEASE SUFENTANIL COMPOSITIONS

The present invention concerns sustained release sufentanil compositions for intramuscular administration, the preparation of said compositions and the use of said compositions for inhibiting pain, in particular post-operative pain, in animals, particularly in companion animals.

Sufentanil is the generic name of *N*-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-*N*-phenylpropanamide and can be represented by the formula



This compound, its acid addition salt forms, preparation and pharmacological properties are known from US-3,998,834. Sufentanil is a potent, short-acting opioid analgesic; 7 to 10 times as potent as fentanyl and 500 to 700 times as potent as morphine. Sufentanil is known to provide cardiovascular stability and attenuation of stress reactions with minimal side-effects and without compromising recovery. In humans, it has been used, intravenously, as an adjunct to nitrous oxide/oxygen in general surgery and at higher doses ($\geq 8 \mu\text{g/kg}$) as a sole anaesthetic in cardiac and neurosurgery.

It is not uncommon that human patients and also animals suffer pain following a surgical procedure. Sufentanil's use for the control of such acute pain in human patients and in animals by conventional or intramuscular or intravenous administration has been limited because of its short duration of action. In human patients, this problem can be overcome by a continuous infusion or by regular injections at fixed intervals of about 2 to 4 hours. However, drawbacks of continuous infusion are for example the need of an infusion device, the need for continuous supervision and the high cost. Most certainly, continuous infusion is impractical, and in many instances not fit, for use in veterinary medicine. Also, the use of intramuscular injections of short-acting opioids at fixed intervals has its handicaps. A common failure of pain relief therapy occurs through the persistent use of shortacting medications on an "as needed" basis. A major disadvantage of this patient-controlled analgesia is that the indication for analgesic therapy (pain) occurs before the drug can be administered. It may then

take time and higher doses of opioids to relieve the pain and usually leads to a cycle of undermedication and pain, alternating with periods of overmedication and drug toxicity. Thus, while intramuscular injection of shortacting opioids is a simple and inexpensive technique, it falls short in achieving an efficacious control of acute pain.

- 5 Moreover, patient-controlled analgesia is impossible in veterinary medicine. Administration of analgesics by the owner or by a veterinarian will seldom be programmed "just-in-time". Other drawbacks of current pain relief therapies include concerns about respiratory depression and drug dependency associated with opioid analgesics.

10

The ideal therapeutic regimen for acute pain relief would be to achieve rapidly therapeutic plasma levels and to maintain these for extended periods (if required) without undue side-effects such as respiratory depression.

- 15 WO-92/02256, published on February 20, 1992, discloses a pharmaceutical composition comprising sufentanil citrate and 2-hydroxypropyl- β -cyclodextrin useful for neuraxial administration. UK patent application GB-2.287,404, published on September 20, 1995, encompasses compositions for the prevention or treatment of pain or inflammatory diseases which comprise a substance P receptor antagonist and an anti-inflammatory or analgesic agent, such as, e.g. sufentanil. WO-95/31182, published on November 23, 1995, discloses formulations, useful for aerosol delivery with a metered dose inhaler, comprising a base form of a narcotic drug such as, e.g. sufentanil, and a propellant. Optionally lubricants such as saturated vegetable oils, e.g. fractionated coconut oils, may be present to lubricate valves in said metered dose inhaler.

25

- The present invention now provides specific pharmaceutical compositions suitable for intramuscular administration, comprising a medium-chain triglyceride as a carrier and as an active ingredient an effective analgesic amount of sufentanil. Said compositions are particularly useful in veterinary medicine and give a constant sustained release of sufentanil over a period ranging from 12 to 48 hours, in particular 24 hours, and retain all advantageous properties of the known short-acting sufentanil compositions. Therapeutic plasma levels can be achieved rapidly and maintained for the above periods.

30

- 35 The term "medium-chain triglyceride" as used hereinabove defines triglycerides of saturated fatty acids, in particular of octanoic (caprylic) and decanoic (capric) acid. Said triglycerides correspond to the requirements laid down in the European Pharmacopoeia EP93 (Triglycerida saturata media), the British Pharmacopoeia BP88

-3-

(Fractionated coconut oil) and the DAB 9 (Mittelkettige Triglyceride). Synonyms for medium-chain triglyceride are, for example, fractionated coconut oil, thin vegetable oil, mittelkettige Triglyceride, triglycerida mediocatenalia and are meant to be comprised under the term "medium-chain triglyceride" as used herein. A particular example of
5 said triglycerides is Miglyol 812®, a substantially colourless, odourless, tasteless, neutral and stable, oil-like liquid with low viscosity. Comparable medium-chain triglycerides are Estasan GT8-40 35/78®, Myritol 318® and the like.

The term "sufentanil" as used in the specification and the claims herein comprises
10 sufentanil in the free base form and in particular the salts thereof which are soluble in medium-chain triglycerides, especially salts of sufentanil with C₈₋₂₂carboxylic acids, including saturated and unsaturated C₈₋₂₂carboxylic acids.

Said C₈₋₂₂carboxylic acids are meant to comprise those carboxylic acids having from 8
15 to 22 carbon atoms such as, for example octanoic (caprylic), nonanoic (pelargonic), decanoic (capric), undecanoic, lauric, tridecanoic, tetradecanoic (myristic), pentadecanoic, hexadecanoic (palmitic), heptadecanoic, octadecanoic (stearic), nonadecanoic, eicosanoic, heneicosanoic and docosanoic acid. Examples of
unsaturated C₈₋₂₂carboxylic acids include oleic, linoleic, linolenic acid and the like.

20 Particular salt forming carboxylic acids are C₈₋₂₂carboxylic acids, preferably myristic, palmitic, stearic and eicosanoic acid, more preferably stearic acid.

Most preferred are compositions wherein sufentanil and stearic acid are formulated in
25 stoichiometric amounts, *i.e.* sufentanil in its (1:1) stearic acid salt form.

In the compositions according to the present invention the concentration of sufentanil in free base form ranges from 0.1 mg/ml to 1 mg/ml, in particular from 0.3 mg/ml to 0.8
30 mg/ml. Preferably, the concentration of sufentanil in free base form is 0.5 mg/ml.

If desired, other active ingredients may be incorporated in the present compositions, such as, for example, antimicrobials, antioxidizing agents or a combination thereof, e.g. methyl parahydroxy benzoate, ethyl parahydroxybenzoate, salicylic acid, benzoic acid, benzyl alcohol, butylhydroxytoluol, butylhydroxyanisole, propylgallate, ascorbyl-
35 palmitate, α -tocopherol and the like. The individual concentration of said other active ingredients in the present compositions is small, in general less than 2% (w/w).

Preferred compositions contain an appropriate amount of an antimicrobial, more in particular, benzyl alcohol, and/or an appropriate amount of an antioxidizing agent such

as, for example, butylhydroxytoluol, butylhydroxyanisole, propylgallate, ascorhyl-palmitate, α -tocopherol or a combination thereof.

- 5 Preferably, BHT (also known as butylated hydroxytoluene, butylhydroxytoluol or 2,6-di-*tert*-butyl-4-methylphenol) is used as an antioxidizing agent in an amount between 0.1 and 1 mg/ml, in particular 0.25 mg/ml.

For preparing the compositions of the present invention, the active ingredient sufentanil in its free base form or in its salt form as defined hereinabove, is intimately mixed with
10 a medium-chain triglyceride. Compositions comprising a salt of sufentanil with a carboxylic acid as defined hereinabove may also be prepared by intimately mixing said carboxylic acid in the medium-chain triglyceride at a temperature ranging between room temperature and 60°C, preferably between 40°C and 50°C, prior to intimately
15 mixing the active ingredient sufentanil in its free base form. Where appropriate, one or more other active ingredients as defined hereinabove may be added to the admixture. The thus obtained solutions are then brought to the final volume by the addition of medium-chain triglyceride as required. The addition of the required amount of the medium-chain triglyceride may also be performed at an earlier time during the preparation procedure. The resulting oil solution of sufentanil may be sterilized by
20 filtration and filled in sterile ampoules. If desired, the resulting oil solution may be filled in said sterile ampoules under an inert atmosphere such as, for example, oxygen-free nitrogen. Optionally, said ampoules may be made of amber colored glass.

- An interesting preparation procedure comprises the following steps
- 25 (a) intimately mixing a carboxylic acid with a medium-chain triglyceride;
(b) intimately mixing sufentanil in free base form with a solution of a carboxylic acid in a medium-chain triglyceride;
(c) intimately mixing one or more active ingredients with a solution of a carboxylic acid and sufentanil in free base form in a medium-chain triglyceride;
30 (d) filtering a solution of a carboxylic acid and sufentanil in free base form and one or more other active ingredients in a medium-chain triglyceride under sterile conditions;
(e) filling a filtered solution of a carboxylic acid and sufentanil in free base form and one or more other active ingredients in a medium-chain triglyceride in sterile
35 ampoules.

The present compositions may be formulated in dosage unit forms or in multi-dose containers. It is especially advantageous to formulate the present compositions in multi-

dose containers. A multi-dose container as used herein refers to a physically discrete container containing between 1 and 10 ml, more preferably between 2 ml and 5 ml, of one of the present compositions, and from which multiple unitary dosages may be taken. A multi-dose container may have the advantage that a physician or a
5 veterinarian can select on the basis of the diagnosis of the subject to be treated the appropriate amount, and if desired, that the multi-dose container may be stored and used afterwards to treat the same or a different subject.

The present invention further relates to the pharmaceutical compositions as defined
10 hereinabove for use as an analgesic. In particular, the present invention relates to the use of the present pharmaceutical compositions for preparing a medicament to treat animals suffering from acute pain, more in particular post-operative pain.

Pain as used herein relates to post-operative pain following surgery, including dental
15 surgery; cancer pain; pain occurring while a veterinary surgeon performs an intervention which does not require general anesthesia such as, for example, in case a veterinary surgeon treats an ear infection; post-traumatic pain and the like instances of acute pain.

20 Thus, the present invention provides a method of inhibiting pain, particularly acute pain, more in particular post-operative pain, in an animal, in particular companion animals, comprising administering intramuscularly to said animal a therapeutically effective amount of a composition as defined hereinabove.

25 The intramuscular injection of the present compositions may be administered just prior to surgery or at the end of surgery, preferably during the early postoperative period. Said injection can conveniently be given in, for example, the musculus gluteus with, for example, the use of an appropriate intramuscular needle with long bevel.

30 Companion animals as used herein are meant to include all animals that are not used for the production of food. Examples of companion animals are dogs, cats and the like.

In order to achieve rapidly therapeutic plasma levels and to maintain these for extended periods (if required) without undue side-effects such as respiratory depression, and,
35 depending on the species, it is contemplated that an effective amount of sufentanil would range from 25 µg/24 h to 25 mg/24 h, preferably from 100 µg/24 h to 10 mg/24 h of the active ingredient sufentanil in free base form, in order to obtain effective analgesia with therapeutic plasma levels in the range of from 0.3 ng/ml to 3 ng/ml, in

- particular from 0.85 ng/ml to 1.5 ng/ml. Taking into account the body weight of the subject to be treated, said required therapeutic plasma levels, and hence, the desired clinical effects can be obtained by administering intramuscularly a dose ranging between 25 µg/kg body weight to 75 µg/kg body weight, preferably a dose ranging between 35 µg/kg body weight to 70 µg/kg body weight, more preferably a dose of 50 µg/kg body weight of the active ingredient sufentanil in base form. Using a composition comprising 0.5 mg/ml of sufentanil in free base form, e.g., an animal weighing about 50 kg should receive about 5 ml of the composition, animals weighing about 5 kg should receive 0.5 ml of the composition. Obviously these doses may be lowered or increased, depending on the severity of the pain, the individual response of the animal and the required duration of effective analgesia. Further, if deemed necessary, the present composition may be administered repeatedly at appropriate intervals, e.g. at 12 hour or longer intervals, preferably at 24 hours intervals.
- Pharmacokinetic studies as presented in the experimental part B hereinafter show that therapeutic plasma concentrations may be obtained soon after injection of a 0.5 mg/ml solution at a dose ranging between 35 µg/kg body weight and 70 µg/kg body weight, and are maintained for up to 48 hours after injection.
- The following examples are intended to illustrate the present invention and not to limit the scope thereof.

Experimental part

A. Preparation of the compositions

25 Formula F.1 : Injectable solution - 0.5 mg/ml

- Miglyol 812® (500 grams) was stirred at 46°C and stearic acid (1.85 grams) was added. Stirring was continued for 30 minutes. While stirring, the solution was diluted with Miglyol 812® (4140 grams). The resulting solution was allowed to cool to room temperature, and sufentanil in its free base form (2.5 grams) was added. Stirring was continued for 16 minutes. Benzyl alcohol (75 grams) was added while stirring at room temperature. The resulting solution containing 0.5 mg/ml of the active ingredient sufentanil was filtered under sterile conditions and filled in sterile ampoules.

Hence, the F.1 formulation has the following composition :

- | | | |
|----------------|------|----|
| 35 Sufentanil | 0.5 | mg |
| Stearic acid | 0.37 | mg |
| Benzyl alcohol | 15 | mg |
| Miglyol 812® | 928 | mg |

-7-

In a similar way, the following compositions were prepared :

Formula F.2 : Injectable solution - 0.4 mg/ml

	Sufentanil	0.4	mg
	Stearic acid	0.294	mg
5	Miglyol 812®	928	mg

Formula F.3 : Injectable solution - 0.2 mg/ml

	Sufentanil	0.2	mg
	Stearic acid	0.147	mg
10	Miglyol 812®	928	mg

Formula F.4 : Injectable solution - 0.5 mg/ml

	Sufentanil	0.5	mg
	Stearic acid	0.37	mg
15	Benzyl alcohol	15	mg
	BHT	0.25	mg
	Miglyol 812®	928	mg

B. Pharmacokinetic studies : Plasma kinetics of sufentanil in beagle dogs after single intramuscular administration of a sustained release formulation of sufentanil.

- 20 *Dosing* Three groups of seven male beagle dogs, weighing between 11 and 20 kg, were used in the experiment. A first group received a single intramuscular dose of 35 mg/kg body weight by injection of a 0.5 mg/ml sufentanil solution in Miglyol 812® (Formula F.1 as described in the experimental part
- 25 A) in the thigh muscle. A second group received under the same conditions a single intramuscular dose of 50 µg/kg body weight, and a third group received under the same conditions a single intramuscular dose of 70 µg/kg body weight. Owing to the precision of the dosing syringe (0.1 ml), administered doses differed less than 1% from the intended dose.
- 30 *Sampling* Blood samples (5 ml on heparin 15-18 IU/ml blood) were taken from a jugular vein from the sufentanil treated dogs. Sampling was performed before (0 hours) and at 15, 30, 45, 60 and 90 minutes and at 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours after dose administration. The blood samples were centrifuged at 3000 rpm for 10 minutes to allow plasma separation.
- 35 *Analysis* Plasma samples were analyzed for sufentanil using a RIA method as described in Woestenborghs *et al.*, Anesthesiology 1994, 80, 666-670. Mean plasma concentrations (in ng/ml) per dose level and per sampling time were calculated and are listed in Table I.

Table 1

Post-dosing time (hours)	plasma concentration per dosage level (ng/ml)		
	35 µg/kg	50 µg/kg	70 µg/kg
0	≤ 0.050	≤ 0.050	≤ 0.050
0.25	0.194	0.532	0.331
0.5	0.342	0.727	0.498
0.75	0.388	0.771	0.600
1	0.478	0.808	0.734
1.5	0.484	0.782	0.839
2	0.575	0.906	1.04
3	0.712	1.05	1.34
4	0.793	1.12	1.67
6	0.929	1.16	2.17
8	0.893	1.13	1.91
12	0.843	1.10	1.61
24	0.440	0.718	0.849
48	0.142	0.205	0.360
72	≤ 0.050	≤ 0.050	0.095

Claims

1. A pharmaceutical composition suitable for intramuscular administration comprising a medium-chain triglyceride as a carrier and as an active ingredient an effective analgesic amount of sufentanil.
2. A pharmaceutical composition according to claim 1 wherein the active ingredient comprises sufentanil in the free base form or a pharmaceutically acceptable salt of sufentanil.
3. A pharmaceutical composition according to claim 1 or 2 wherein the active ingredient comprises a salt of sufentanil with a C₈₋₂₂carboxylic acid.
4. A pharmaceutical composition according to any one of claims 1 to 3 wherein the active ingredient is the salt of sufentanil with stearic acid.
5. A pharmaceutical composition according to any one of claims 1 to 4 wherein the active ingredient is the (1:1) salt of sufentanil with stearic acid.
6. A pharmaceutical composition according to any one of claims 1 to 5 wherein the concentration of sufentanil in free base form ranges from 0.1 mg/ml to 1 mg/ml.
7. A pharmaceutical composition according to any one of claims 1 to 5 wherein the concentration of sufentanil in free base form ranges from 0.3 mg/ml to 0.8 mg/ml.
8. A pharmaceutical composition according to any one of claims 1 to 5 wherein the concentration of sufentanil in free base form is 0.5 mg/ml.
9. A pharmaceutical composition according to any one of claims 1 to 8 also comprising an antimicrobial or an antioxidizing agent, or a combination thereof.
10. A pharmaceutical composition according to claim 9 wherein the antimicrobial is benzyl alcohol.
11. A pharmaceutical composition according to claim 9 wherein the antioxidizing agent is BHT.
12. A pharmaceutical composition according to any one of claims 1 to 11 wherein the medium-chain triglyceride is Miglyol 812®.

-10-

13. A process for preparing a pharmaceutical composition as defined in any one of claims 1 to 12, characterized in that a therapeutically effective amount of sufentanil is intimately mixed with the medium-chain triglyceride.
- 5 14. A process according to claim 13 whereby a carboxylic acid and sufentanil in free base form, are intimately mixed with the medium-chain triglyceride.
- 15 15. A process according to claim 13 comprising the following steps :
- 10 (a) intimately mixing a carboxylic acid with a medium-chain triglyceride;
- (b) intimately mixing sufentanil in free base form with a solution of a carboxylic acid in a medium-chain triglyceride;
- (c) intimately mixing one or more active ingredients with a solution of a carboxylic acid and sufentanil in free base form in a medium-chain triglyceride;
- 15 (d) filtering a solution of a carboxylic acid and sufentanil in free base form and one or more other active ingredients in a medium-chain triglyceride under sterile conditions;
- (e) filling a filtered solution of a carboxylic acid and sufentanil in free base form and one or more other active ingredients in a medium-chain triglyceride in
- 20 sterile ampoules.
16. Sufentanil stearic acid salt (1:1).
17. The use of a pharmaceutical composition as defined in any one of claims 1 to 12
- 25 for the manufacture of a medicament to treat animals suffering from pain.
18. The use of a pharmaceutical composition according to claim 17 wherein the pain is post-operative pain.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/03236

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/445 A61K47/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 02256 A (UNIVERSITY OF CALIFORNIA) 20 February 1992 cited in the application see claims ---	1-18
A	GB 2 287 404 A (PFIZER) 20 September 1995 cited in the application see page 3, line 30 - page 4, line 4 see claims ---	1-18
A	WO 95 31182 A (ARADIGM) 23 November 1995 cited in the application see claims see page 15, line 24 - line 28 -----	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

24 September 1997

Date of mailing of the international search report

13.10.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No

PCT/EP 97/03236

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9202256 A	20-02-92	US 5180716 A AU 8404991 A	19-01-93 02-03-92
GB 2287404 A	20-09-95	NONE	
WO 9531182 A	23-11-95	AU 2478695 A CA 2189351 A EP 0759744 A	05-12-95 23-11-95 05-03-97